Form: PTO/SB/17 (Modified)

REPLY/AMENDMENT FEE TRANSMITTAL

Attorney Docket No.	662-57773
Application Number	09/915,549
Filing Date	07/27/2001
First Named Inventor	Muller
Group Art Unit	1615
Examiner Name	Sheikh

AMOUNT ENCLOSED | $

FEE CALCULATION (fees effective 10/01/97)

CLAIMS AS AMENDED	Claims Remaining After Amendment	Highest Number Previously Paid For	Number Extra		Rate	Calculations
TOTAL CLAIMS	150	150	0	(3)	X $18.00 =	
INDEPENDENT CLAIMS	3	3	0		X $78.00 =	

Since an Official Action set an original due date of 12/12/2003 , petition is hereby made for an extension to cover the date this reply is filed for which the requisite fee is enclosed (1 month ($110); 2 months ($400); 3 months ($950); 4 months ($1,510); 5 months ($2,060)): 2 Months	420
If Statutory Disclaimer under Rule 20(d) is enclosed, add fee ($110)	+
Total of above Calculations =	$420
Reduction by 50% for filing by small entity (37 CFR 1.9, 1.27 & 1.28)	-210
TOTAL FEES DUE =	$210

(1) If entry (1) is less than entry (2), entry (3) is "0".
(2) If entry (2) is less than 20, change entry (2) to "20".
(4) If entry (4) is less than entry (5), entry (6) is "0".
(5) If entry (5) is less than 3, change entry (5) to "3".

METHOD OF PAYMENT

[X] Check enclosed as payment.

[ ] Charge "TOTAL FEES DUE" to the Deposit Account No., below.

AUTHORIZATION

[X] If the above-noted "AMOUNT ENCLOSED" is not correct, the Commissioner is hereby authorized to credit any overpayment or charge any additional fees under 37 CFR 1.16 or 1.17 necessary to maintain pendency of the present application to:

Deposit Account No.:	50-0687
OrderNo.: (Client/Matter)	62662

SUBMITTED BY: Manelli, Denison & Selter, PLLC

Typed Name	Jeffrey S. Melcher	Reg. No.	35,950
Signature		Date	February 5, 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT Application of Muller

Group Art Unit: 1615

Application No. 09/915,549

Examiner: Humera N. Sheikh

Filed: July 27, 2001

For: DISPERSIONS FOR THE FORMULATION OF SLIGHTLY OR POORLY SOLUBLE AGENTS

* * * * *

February 5, 2004

RESPONSE UNDER RULE 116

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is in response to the Final Office Action dated September 12, 2003.

Reconsideration and allowance of the subject application are respectfully requested.

Claims 1-150 are pending in the application. Claims 16-18, 67-142, 145 and 147 stand withdrawn pursuant to a restriction requirement.

From the Examiner's comments regarding the prior art rejections, it is clear that the claimed creation of **supersaturated** emulsions (i.e. producing emulsions which contain a drug concentration being well above the maximum soluble combined amount of the water and the oil phase) and the exclusion of organic solvents was once again improperly dismissed.

The terms "saturation solubility" and "supersaturated systems" are well-known by those of ordinary skill in the art as follows:

The saturation solubility is the maximum concentration of a compound in a liquid at a certain temperature and excess compound will be present in form of a non-dissolved precipitate. In case a system consists not only of one liquid but two (e.g. emulsion consisting of water and oil), the total saturation solubility (saturation concentration) of the system (emulsion) is the addition of the saturation solubilities in each of the liquids.

In a supersaturated system, the drug concentration dissolved **is above the**

saturation solubility. Such systems can be formed for example when a saturated solution is cooled. The drug does not yet precipitate despite that its concentration is above the saturation solubility, because of the lack of crystallization cores. Such supersaturated systems have pharmaceutical benefits but are in general metastable and very critical to achieve, that means they exist for a short time, often only minutes before the drug crystallizes out of solution.

When simply dissolving a drug, e.g., in an oil (as done by Kaufmann when dissolving paclitaxel), only systems at the saturation solubility can be obtained. **Routine experimentation by simply trying to dissolve different concentrations in the oil will not lead to a stable supersaturated system**.

The present invention relates to novel supersaturated systems that are prepared by novel claimed preparation processes. The drug concentrations in the systems of the present invention are well above the saturation solubility obtained by prior art methods.

A typical example of a poorly soluble drug is Amphotericin B. The limitation in solubility leads to undesirably large injection volumes, or in many cases reaches volumes too large to be administered to a patient. An example is the maximum solubility of Amphotericin B (1mg/mL) in the o/w emulsion, such as in the presently cited Davis. The present invention allows the incorporation of drugs in concentrations above the saturation solubility of the drug in the emulsion (total solubility = amount of drug in water plus amount of drug in oil). The present invention allows one to reach supersaturation in the emulsions, i.e. going beyond the previously known maximum solubilities. For example, instead of 1 mg/ml (maximum solubility in oil/water), the incorporated amount can now be doubled to a concentration of 2mg/ml (supersaturation). In variants of the invention, concentrations of 5-10mg/mL can even be achieved. None of the cited references anticipates, teaches or suggests such supersaturation or formation of drugs that are also organic solvent-free.

Furthermore, oil and water emulsions have been used since the seventies to deliver drugs intravenously. The drugs are typically dissolved in the oil of the emulsion, such as the presently cited Kaufmann. Kaufmann even uses solvents to

facilitate dissolution in the oils. Alternatively drugs can be incorporated via a lecithin blend using organic solvents. The present invention does not use organic solvents, and therefore the product is organic solvent-free. In contrast, the cited prior art uses and contains organic solvents.

The rejection of claims 1-15, 19-25, 33-35, 37-46, 48, 55-57, 61-63, 143, 144, 146 and 148 under 35 U.S.C. § 102(b) as being anticipated by EPO 0 296 845 (Davis) is respectfully traversed. The claimed invention is not anticipated by Davis for the following reasons.

The first difference between the present invention and Davis is that Davis needs to use organic solvents to produce the emulsion. Consequently even after removal of the solvent by classical, well-known means a residue of solvent will remain in the emulsion, which can cause toxicological problems and even may prevent registration with the authorities in case the contamination level is too high. In addition, removal of the organic solvent is a costly process. The claimed invention is organic solvent-free because no organic solvents are used in the production process. This is pointed out in claim 1 as characteristic feature of the product. The product by Davis always contains solvent residues, even when they are only in the lower ppm concentration range.

The Examiner argues on page 11 of the Office Action that:

> Furthermore, Davis also teaches removing **at least most of** any co-solvent that is present. Additionally, one of ordinary skill in the art would be able to determine suitable solvents, which would not be deemed detrimental to the formation itself. Furthermore, the applicant's arguments that 'no organic solvents are used in the production process' is not persuasive since the instant pending claims are composition claims and it is the patentability of the composition itself that must be established. Davis teaches a **similar** composition for a **similar** intended purpose as the applicants. (emphasis added)

The Examiner basically admits that Davis does not anticipate the claimed invention, but rather only teaches a "similar" composition. A rejection under Section 102 requires more than disclosure of mere similarities: it requires disclosure of "every aspect of the claimed invention either explicitly or impliedly." See MPEP § 706.02(a). The Examiner has not shown how Davis teaches explicitly or impliedly

to make a composition (1) containing no organic solvents or even residues of organic solvents, and (2) a supersaturation amount of drug.

Furthermore, Applicant did not merely argue process limitations. Instead, Applicant argued that the presently claimed invention does not contain any organic solvents, or organic solvent residues, because there are no organic solvents used to prepare the composition. This argument goes right to the patentability of the claimed composition, "no organic solvent residues present."

The Examiner's argument that "one of ordinary skill in the art would be able to determine suitable solvents, which would not be deemed detrimental to the formation itself" is immaterial and demonstrates that the Examiner admits that organic solvents are present in the composition of Davis. The Examiner also admitts that Davis teaches that the composition contains organic residues by arguing that "at least most of the co-solvent" in Davis removed. A composition that contains organic residues cannot anticipate the claimed invention, which excludes such organic residues.

Moreover, in a pharmaceutical formulation the excipients should have a tolerability as high as possible. Based on this approach, it is in any case better to use no solvent at all than using one – independent whether its toxicity is low or not. Nevertheless, the Examiner's reliance on weather the organic solvent is detrimental is immaterial to a patentability determination under Section 102.

The use of "comprising" in claim 1 does not bring back into the claim what is specifically excluded by the claim language. For the Examiner to now argue that use of "comprising" overrides or trumps all other claim language would overturn over 100 years of patent law.

The Examiner argues on pages 11 and 12 of the Office Action that:

> The applicants argument that the instant invention allows the incorporation of the drug beyond the concentration soluble in the oil and water phase of the emulsion was not found to be persuasive, since Davis explicitly teaches emulsions that are stable and reduce the toxicity of the drug.
>
> The applicants arguments regarding the maximum concentrations of drug being soluble are also not persuasive, since generally, differences in concentration (or temperature) will not support the patentability of

> subject matter encompassed by the prior art unless there is evidence indicating such concentration (or temperature) is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). The prior art clearly recognizes the generic concept of formulation a stable oil-in-water emulsion comprising poorly soluble active ingredients.

Applicant respectfully submits that the present invention is not mere optimization as alleged by the Examiner. One of ordinary skill in the art cannot optimize what is not taught. If the prior art teaches that the maximum concentration of a drug is 1 ppm, one skilled in the art would not ignore this teaching and "optimize" the concentration of the drug to be greater than 1 ppm, i.e. outside the concentration limit of the drug. Essentially, the Examiner is arguing that one skilled in the art would ignore teachings in Davis to use the maximum concentration level, and now use a supersaturation concentration outside of those teachings. This is contrary to patent law. Those skilled in the art follow the teachings of the prior art, they do not do the opposite of what the prior art teaches as alleged by the Examiner.

In fact, Davis teaches in a direction away from the claimed invention. Davis teaches to use only the maximum concentration level. In contrast, the claimed invention teaches a composition containing supersaturation levels of drug.

The Examiner states there is no evidence that supersaturation levels are critical. This argument by the Examiner will be addressed in response to the Section 103 rejection below since it is immaterial in a Section 102 rejection.

According to Davis a concentration of 0.5 mg/l can be achieved when using 1.2% lecithin and 10% soya oil in the emulsion (90ml mixture of water, lecithin and drug plus 10 ml oil, Example 1). The loading can be increased to 1 mg/ml when increasing the lecithin to 1.8% and the oil to 20%. These concentrations represent the maximum amount of drug being soluble in the oil and water phase, i.e. the saturation solubility of the drug in these emulsions.

In contrast, the present invention allows the incorporation of the drug beyond the concentration soluble in the oil and water phase of the emulsion. Even when using only 1.2% lecithin, the present invention can incorporate 2mg/ml Amphotericin

B. The present invention can use a concentration above the saturation solubility and double the amount which can be achieved by Davis even when using the higher lecithin concentration of 1.8%.

The present invention creates supersaturated emulsions, which are not disclosed in Davis. On the contrary, Davis teaches clear limits for the maximum drug incorporation. For this reason alone, Davis cannot anticipate the claimed invention.

In view of the admitted differences between Davis and the claimed invention, the claimed invention cannot be anticipated by Davis and withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1-11, 19-25, 33-35, 37-45, 48, 55-57, 61-63, 143, 144, 146 and 148 under 35 U.S.C. § 102(b) as being anticipated by U.S. patent No. 5,616,330 (Kaufman) is respectfully traversed. The claimed invention is not anticipated by Kaufman for the following reasons.

The Examiner argues on page 10 of the Office Action that:

> The applicant's arguments that organic solvents are not excluded in Kaufmann was not found to be persuasive since one of ordinary skill in the art would be able to determine acceptable or suitable solvents and one of ordinary skill in the art would be able to differentiate between ingredients that may or may not be detrimental to the formulation itself. Since Kaufmann utilizes pharmaceutically acceptable solvents in a stable oil-in-water emulsion and also teaches that his formulation provides for a stable emulsion having **minimal side effects**, it would be recognized that these solvents would not, in effect or nature, be toxicologically dangerous to the formulation. Furthermore, the examiner notes that the instant claims use "comprising" claim language, and hence permits the use of additional components asides from those recited in the claims. (emphasis added)

First, Applicant once again points out that the use of "comprising" in claim 1 does not bring back into the claim what is specifically excluded by the claim language. For the Examiner to now argue that use of "comprising" overrides or trumps all other claim language would overturn over 100 years of patent law.

The "minimal side effects" stated by the Examiner are completely avoided in the claimed composition because there are no organic solvents used in the production of claimed composition and, thus, there are no organic solvents or even

residues of such organic solvents present in the composition. The Examiner basically admits that Kaufmann teaches a composition containing the organic solvents. For this reason alone, Kaufmann cannot anticipate the claimed invention, which does not contain such organic solvents.

The fact that "one of ordinary skill in the art would be able to differentiate between ingredients that may or may not be detrimental to the formulation itself" is immaterial to weather Kaufmann anticipates the claimed invention.

On pages 12 to 13 of the Office Action, the Examiner argues that:

> Kaufmann discloses stable oil-in-water emulsions for intravenous administration incorporating a poorly soluble drug (taxol) in combination with suitable oils, emulsifiers, additives and water. It is deemed obvious to one of ordinary skill in the art to effectively distinguish between ingredients that may or may not be detrimental to the formulation itself. Since Kaufmann utilizes pharmaceutically acceptable solvents in a stable oil-in-water emulsion and also teaches that his formulation provides for a stable emulsion having minimal side effects, it would be recognized that these solvents would not, in effect or nature, be toxicologically dangerous to the formulation. Hence, the applicants arguments that solvents are incorporated in the invention of Kaufmann is not persuasive. The applicants arguments regarding the maximum concentrations of drug being soluble are also not persuasive, since generally, differences in concentration (or temperature) will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration (or temperature) is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." The prior art clearly recognizes formulations of stable oil-in-water emulsions, which comprise poorly soluble active ingredients and therefore, the incorporation of solvents would not adversely affect the composition.

The Examiner plainly admits that Kaufmann's composition contains organic solvents. In contrast, the claimed invention excludes these organic solvents. The Examiner's explanations as to why Kaufmann contains these organic solvents is immaterial to a Section 102 rejection. As stated previously, a rejection under Section 102 requires more than disclosure of mere similarities: it requires disclosure of "every aspect of the claimed invention either explicitly or impliedly." See MPEP § 706.02(a). The Examiner has not shown how Kaufmann teaches explicitly or

impliedly to make a composition containing (1) no organic solvents or even residues of organic solvents, and (2) supersaturation of a drug. For this reason alone, the Examiner has not presented a prima facie case of anticipation and the Section 102 rejection should be withdrawn.

Applicant again respectfully submits that the present invention is not mere optimization as alleged by the Examiner. One of ordinary skill in the art cannot optimize what is not taught. If the prior art teaches that the maximum concentration of a drug is 1 ppm, one skilled in the art would not ignore this teaching and "optimize" the concentration of the drug to be greater than 1 ppm. Essentially, the Examiner is arguing that one skilled in the art would ignore teachings in Kaufmann to use the maximum concentration level, and now use a supersaturation concentration outside of those teachings. This is contrary to patent law. Those skilled in the art follow the teachings of the prior art, they do not do the opposite of the prior art.

In fact, Kaufmann teaches in a direction away from the claimed invention. Kaufmann teaches to use only the maximum concentration level. In contrast, the claimed invention teaches a composition containing supersaturation levels of drug.

The Examiner states there is no evidence that supersaturation levels are critical. This argument by the Examiner will be addressed in response to the Section 103 rejection below since it is immaterial in a Section 102 rejection.

In view of the many differences between Kaufmann and the claimed invention, Kaufmann cannot anticipate the claimed invention and withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1-15, 19-66, 143, 144, 146 and 148 under 35 U.S.C. ' 103 as being unpatentable over Davis alone or Kaufman alone is respectfully traversed. The claimed invention is not taught or suggested by either of Davis or Kaufman for the following reasons.

The Examiner argues in regards to the Section 102 rejections above that there is no evidence that supersaturation levels are critical. Applicant once again points out the criticality of the claimed invention, which is not taught or suggested by the cited prior art.

According to the present invention, it is surprisingly possible to enter the supersaturated concentration range without precipitation of drug crystals during storage. This is achieved by the novel production technology discovered and disclosed in the present application, for example, co-homogenization of drug powder and oil in water. In contrast, it is well known throughout the art, that supersaturation of drugs in a carrier provides an unstable composition in which the drug crystallizes out of solution over time. The cited references are in agreement with this by only teaching to use compositions containing drugs at there solubility limit.

Furthermore, at supersaturation levels, the claimed invention is able to provide a dose containing far less carrier than the prior art compositions. Thus, any undesirable effects due to the carrier are substantially reduced in the present invention.

Moreover, the claimed composition does not contain any organic solvents. In contrast the cited prior art contains organic solvents. Even the "minimal side effects" caused by the organic solvents alluded to by the Examiner are completely avoided by the present invention.

Davis:

On page 14 of the Office Action, the Examiner argues that:

> Davis teaches an oil-in-water emulsion which provides long-term stability. It is the patentability of the composition, per se that must be established. Davis recognizes the concept of intravenous delivery of poorly soluble drugs and teaches the effective delivery of non-toxic amounts of emulsion. One of ordinary skill in the art would be able to determine suitable saturation concentrations through the use of routine or manipulative experimentation, based on the intended purpose, since these are viewed as variable parameters.

Davis teaches clear limits to the drug concentrations, i.e. the solubility of the drug. For example, Davis discloses up to 1 mg/ml, preferably 0.5mg/ml of Amphotericin (column 4, lines 14-16). Davis only teaches to dissolve the drug in amounts up to the saturation concentration of the drug in the oil and water.

In contrast, the claimed composition provides supersaturated concentrations of drug, such that the drug crystals do not precipitate out of solution over time. The

Examiner does not provide any evidence or convincing argument that one of ordinary skill in the art would now ignore the teachings of Davis and go above the saturation limits of the drug and provide a stable supersaturated drug.

Once again, Applicant submits that it is not routine experimentation to ignore teachings of the prior art and use concentrations outside of the disclosed ranges as alleged by the Examiner, especially not supersaturation concentrations that are well-known to be unstable. For this reason alone, the Section 103 rejection should be withdrawn.

The Examiner essentially argues on pages 4-6 of the Office Action that known emulsions using similar compositions of excipients can be administered by the same routes and have similar sizes. However, this does not apply to drugs for the reasons discussed below.

The Examiner denies any significant distinction between Davis and the present invention. A main difference overlooked by the Examiner is the achieved drug loading: (1) the saturation concentration with Davis and Kaufmann; and (2) in the supersaturation range in the present invention.

According to the Examiner, Davis teaches similar amounts of drug incorporated in the suspension compared to the present invention (page 6, third paragraph of Office Action). Davis discloses up to 1 mg/ml, preferably 0.5mg/ml of Amphotericin (column 4, lines 14-16). Davis only teaches to dissolve the drug in amounts up to the saturation concentration of the drug in the oil and water. In the present invention, going beyond this saturation limit and even doubling the saturation solubility is unexpected and something which was not predictable from Davis. Davis does not teach supersaturation of drugs. The instant invention can, for example, produce emulsions with 5mg/ml Amphotericin (supersaturated), Davis cannot.

Applicant believes the invention works in the following manner but is not bound by this theory. Applicant's belief about the mechanism have been submitted for publication to the Int. J. Pharm. The drug is believed to be not molecularly dispersed in the lecithin layer, and it seems to form "molecular nano-arrangements," which allow a much higher drug incorporation than molecular dissolution in the

lecithin. These special arrangements in the interfacial layer are generated by the novel production method disclosed in the present application. It is speculated that the high energy input in the presence of a high drug concentration leads to the formation of such nanostructures and increased loading capacity. Previously, homogenization with such high drug concentration was not tried because it appeared to be nonsense. It was expected that drug concentrations above the saturation solubility in the emulsion could not be incorporated and would remain as sediment. Just the opposite was surprisingly found in the instant invention.

Applicant respectfully submits that the Examiner is not correct in stating that the prior art teaches suitable concentration to arrive at stable emulsions. The prior art concentrations are not sufficiently high to obtain acceptable injection volumes. The previous emulsions are at the or even below the saturation concentration, i.e. they are not supersaturated emulsions. The emulsions of the invention are also stable, but the key feature is the supersaturation, which provides suitable injection volumes.

Applicant submits that it is unfair for the Examiner to compare the stability of a drug composition disclosed in Davis, in which the drug is present at a concentration at or below the solubility limit, with the present invention, in which the drug is present at a concentration above the solubility limit. Of course, the drug will remain in solution if it is at or below it solubility limit. That is the definition of solubility. However, it is now quite unexpected that a drug can be stabilized above its solubility limit in the claimed composition.

Kaufmann:

On pages 14 to 15 of the Office Action, the Examiner argues that:

> The teachings of Kaufmann have been discussed above. Kaufmann teaches stable oil-in-water emulsions for poorly soluble active ingredients. The applicants arguments that there is no teaching in either reference to exclude the use of organic solvents is not persuasive since the instant claims use "comprising" claim language, and thus the incorporation of additional ingredients, asides from those recited are not excluded from the claims. The prior art teaches stable emulsions incorporating solvents, however, since these solvents are routinely used in the pharmaceutical art, they would not be considered

detrimental or toxic to the formulation. Hence, the instant invention is rendered obvious and unpatentable over the prior art.

Applicant once again points out that the use of "comprising" in claim 1 does not bring back into the claim what is specifically excluded by the claim language. For the Examiner to now argue that use of "comprising" overrides or trumps all other claim language would overturn over 100 years of patent law.

The Examiner's argument that "since these solvents are routinely used in the pharmaceutical art, they would not be considered detrimental or toxic to the formulation" is immaterial. Any side effects due to organic solvents is detrimental to the patient. In the present invention, all side effects due to organic solvents are avoided since no organic solvents are present. The prior art does not teach or suggest avoiding all side effects by using a composition containing no organic solvents.

The Examiner points out the different excipients used by Kaufmann and also the different taxines. Kaufmann teaches the amount of 0.1% to 1% taxine in the emulsions which, according to the Examiner, are in the range of the present invention.

However, one cannot compare incorporation of one drug (Amphotericin) directly with another drug (in this case taxine). It might be easy to incorporate drug A (e.g. taxine) in a concentration of 1% in case the saturation solubility in the emulsion is well above, e.g. 5%. However, even when incorporating 1% of drug B, this represents a major achievement when the saturation solubility of B is only e.g. 0.1%. From this, direct comparison on the basis of just percentages is not possible. The solubility of each drug must also be considered.

Furthermore, according to the present invention, concentrations of 5 and 10mg/ml can be incorporated, the latter by using an emulsion with crystalline fraction.

In addition, Kaufmann clearly teaches using Cholesterol to solubilize the drug. This means that Kaufmann is working with an oil phase at the maximum solubility. The instant invention is working well above the saturation solubilities. In contrast to Kaufmann, the present invention is a supersaturated system.

As discussed above, the supersaturated system according to the present invention is unexpected and provides many advantages over the conventional maximum solubility system of Kaufmann.

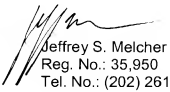
Applicant submits that it is unfair for the Examiner to compare the stability of a drug composition disclosed in Kaufmann, in which the drug is present at a concentration at or below the solubility limit, with the present invention, in which the drug is present at a concentration above the solubility limit. Of course, the drug will remain in solution if it is at or below it solubility limit. That is the definition of solubility. However, it is now quite unexpected that a drug can be stabilized above its solubility limit in the claimed composition.

Furthermore, both Davis and Kaufmann teach using organic solvents, which are excluded by the present invention. There is no teaching in either reference to exclude the use of organic solvents.

In view of the many differences between the present invention and Davis or Kaufmann, and the many unexpected advantages of the present invention, withdrawal of the Section 103 rejection is respectfully requested.

In view of all of the rejections of record having been addressed, Applicant believes the application to be in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,
Manelli Denison & Selter PLLC

By 

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